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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,735	11/19/2003	Christopher R. Wagstrom	37210-8004.US00	8693

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EXAMINER	
STEELE, AMBER D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,735	WAGSTROM ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *5,7-10,12,14,15,22-24,27,28,32-34 and 36-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 11, 13, 16-21, 25-26, 29-31, and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-38 are currently pending and under consideration.

Claims 39-40 were cancelled by Applicants in the amendment received on August 29, 2005.

Claims 41-81 were cancelled by Applicants in the preliminary amendment received on November 11, 2003.

Election/Restrictions

2. Applicant's election without traverse of Group I (claims 1-38) in the reply filed on August 29, 2005 is acknowledged.

3. Claims 39-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 29, 2005. Furthermore, applicants cancelled claims 39-40 in the reply filed on August 29, 2005.

4. Applicant's election without traverse of the following species: M13 for the species of expression vector, bacteriophage as the species of host, the variable and constant domains of an antibody light chain as the species of first polypeptide segment and having an OmpA leader sequence but not having a suppressible nonsense codon, a cleavable peptide sequence not having a suppressible codon and located between the first and third segments as the species of second polypeptide segment, a variable and constant domain of an antibody heavy chain not having a leader sequence or a suppressible nonsense codon as the species of third polypeptide segment, a disordered region cleavable by urokinase as the species of cleavable peptide sequence, urokinase

expressed in a **different expression vector** as the species of proteolytic agent, and coat protein III as the species of anchoring sequence in the reply filed on August 29, 2005 is acknowledged.

The Applicants election of a bacteriophage as the species of host appears to be in error since the bacteriophage is the expression vector. In order to expedite prosecution, the host has been determined to be *E. coli* based on the ability of the M13 bacteriophage to infect *E. coli*, claim 25, and the withdrawal of claim 23 by applicants in the reply filed on August 29, 2005.

Furthermore, Applicants election of the proteolytic agent being expressed in a **different** expression vector other than the expression vector presently claimed contradicts the presently claimed invention (i.e. **an** expression vector as presently claimed is a **single** expression vector; please refer to the reply received on August 29, 2005). The election of the proteolytic agent (i.e. urokinase) **being** expressed in a **different** expression vector is not considered, therefore, the claims drawn to the proteolytic agent being expressed in a **different expression vector** are withdrawn (see section 5 below).

5. Claims 5, 7, 8, 9-10, 12, 14-15, 22-24, 27-28, 32-34, and 36-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to **nonelected species**, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 29, 2005.

Drawings

6. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(4) because reference character "77" has been used to designate both the second polypeptide and the linker in Figure 4A. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing

sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

7. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: 30, 32, 35-36, 38, 40, and 42 of Figure 2; 50-52, 54-58, 60, and 62 of Figures 3A-3B; 70-71, 76, 79, and 82 of Figures 4A-4B. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

8. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or

other form of browser-executable code. See MPEP § 608.01. Please refer to page 26 of the Specification.

Claim Objections

9. Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 16 is drawn to a "cleavable peptide sequence not found in either the first or third polypeptide segments and is recognized as a protein cleavage site by a proteolytic agent" and claim 1 is drawn to a "first polypeptide segment, a second polypeptide segment having a cleavable peptide sequence cleavable by a proteolytic agent, and a third polypeptide segment having an anchoring peptide sequence". Therefore, claim 1 states that the cleavable peptide sequence is in the second polypeptide segment and not in the first or third polypeptide segments.

Claim Interpretation

10. The presently claimed invention is directed to:

An expression vector comprising a vector segment encoding:

i. a first polypeptide segment,

ii. a second polypeptide segment having a cleavable peptide sequence, and

iii. a third polypeptide segment having an anchoring peptide sequence.

The limitation that the cleavable peptide sequence in the second polypeptide segment is cleavable by a proteolytic agent is considered to be a functional limitation only. In addition, the limitation that the anchoring peptide sequence in the third polypeptide segment anchors the multimeric polypeptide to the surface of a genetically replicable package is considered to be a functional limitation only. Furthermore, the limitation that the first polypeptide segment

associates with the third polypeptide segment to form a multimeric polypeptide is considered to be a functional limitation only.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993.

Ladner *et al.* teach binding proteins displayed on the outer surfaces of filamentous phage or cells (please refer to column 1, lines 40-52). Ladner *et al.* teach that the display system may be utilized to develop antibodies (please refer to column 15, lines 65-68) as further evidenced by Ladner *et al.* (U.S. Patent No. 4,949,778 issued August 7, 1990; column 8, lines 62-67, column 15, lines 45-52, column 33, lines 56-68, and column 34, lines 1-57). In addition, Ladner *et al.* teach V_L-linker-V_H as single-chain antigen-binding fragment and V_L-C_L bound to V_H-C_{H1} as fragment antibodies (e.g. present claims 1-4 and 6; please refer to column 15, lines 34-64). Furthermore, Ladner *et al.* teach the display system as a binding domain operably linked to a signal sequence (e.g. OmpA and present claim 17; please refer to column 61, lines 39-53, column 62, lines 31-33, and column 63, lines 28-48) and a coat protein (e.g. M13 gene III and present claims 18 and 25; please refer to column 51, line 51 and column 54, lines 48-50) so that

the expression product is transported to the inner membrane of the host cell (e.g. *E. coli* and present claims 25 and 35; please refer to column 56, lines 6-14 and column 61, lines 21-23) and trapped until the single-stranded DNA of the nascent phage particle collects both the wild type coat protein and the hybrid protein from the lipid bilayer and packages the hybrid protein into the surface sheath of the filamentous phage (e.g. M13 and present claims 19-21 and 25-26; please refer to column 54, lines 37-38 and column 55, lines 36-60) thereby exposing the hybrid protein on the replicable genetic package (please refer to column 51, lines 33-68 and column 52, lines 1-11). Lander *et al.* also teach the use of flexible linkers that encode a recognition site for a specific protease including Factor Xa (e.g. present claims 11, 13, 16 and 30-31, please refer to column 57, lines 39-59, column 58, lines 1-18, column 70, lines 64-68, column 71, lines 1-5, and column 73, lines 20-40). Therefore, one of ordinary skill in the art would have anticipated the present invention of claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 in view of the teachings of Ladner *et al.*

13. Claims 1-4, 6, 11, 13, 16-21, 25-26, 30, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffiths *et al.* U.S. Patent No. 5,962,255 issued October 5, 1999.

Griffiths *et al.* teach methods and recombinant host cells for the production of antibodies displayed on the surface of replicable genetic display packages or rgdps (e.g. filamentous phage) via vectors comprising nucleic acids encoding a first and second polypeptide for a specific binding pair or sbp (please refer to the "Abstract"). Griffiths *et al.* also teach the first polypeptide as the variable and constant regions of an antibody light chain (e.g. V_L and C_L), the second polypeptide as the variable and constant regions of an antibody heavy chain (e.g. V_H and C_H or V_H and C_{H1}) with a g3 anchoring peptide (e.g. pIII, gIII, or coat protein III; present claims 18 and

25), and an intervening sequence encoding a selectable "marker peptide" and a loxP site (e.g. a first polypeptide encoding V_L/C_L, a second polypeptide with a cleavable sequence, and a third polypeptide encoding V_H/C_H having an anchor peptide of present claims 1-4, 6, 16, 18, 25, and 30; please refer to Figures 3-4, 6-7, 14-19 and columns 19-21, 24, and 28). Griffiths *et al.* also teach the Cre recombinase which cleaves the loxP site of the intervening sequence and is expressed in a separate plasmid (e.g. enzymatic proteolytic agent of present claims 11, 13, and 30; please refer to column 52, lines 45-55 and column 53, lines 19-24). In addition, Griffiths *et al.* teach that the replicable genetic display package can be a M13 bacteriophage or *E. coli* infected with an M13 bacteriophage (e.g. present claims 19-21, 25-26, and 35; please refer to column 7, lines 52-60, column 22, lines 59-67, and column 24, lines 3-35). Furthermore, Griffiths *et al.* teaches that a secretory leader peptide such as OmpA can be utilized to display the polypeptides (e.g. present claim 17; please refer to column 22, lines 65-66). Therefore, one of skill in the art would have anticipated the present invention of claims 1-4, 6, 11, 13, 16-21, 25-26, 30, and 35 in view of the teachings of Griffiths *et al.*

14. Claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Wang *et al.* U.S. Paten No. 6,833,441 B2 filed August 1, 2001.

Wang *et al.* teach recombinant polynucleotides, vectors, and host cells for producing antigen-binding units (e.g. present claim 35; please refer to the "Abstract"). Wang *et al.* teach a light chain variable region fused to a heterodimerization sequence (e.g. first polypeptide), a "flexon" (e.g. second polypeptide), a heavy chain variable region fused to a second hetrodimerization sequence (e.g. third polypeptide) in a phage display vector and a host cell (e.g. present claims 1-3; please refer to column 4, lines 21-30, column 5, lines 48-61, column 6, lines

45-63,column 20, lines 1-15, column 26, lines 54-64, and column 38, lines 1-39). Additionally, Wang *et al.* also teach V_L, V_H, C_L, C_H, and C_{H1} (e.g. present claims 4 and 6; please refer to column 12, lines 3-10). In addition, Wang *et al.* teach the phage display vector as the filamentous phage M13 and fusion of antibody peptides to a phage coat protein specifically pIII of M13 (e.g. present claims 18-21 and 25-26; please refer to column 13, lines 47-52 and column 29, lines 49-65). Furthermore, Wang *et al.* also teach the use of OmpA for display in bacterial host cells including *E. coli* (e.g. present claim 17 and 25; please refer to column 30, lines 39-49 and column 35, lines 16-22). Moreover, Wang *et al.* teach protease cleavage sites between the heterodimerization sequences and phage coat protein (e.g. present claims 11, 13, 16, and 30-31; please refer to column 37, lines 1-7). Therefore, one of skill in the art would have anticipated the present invention of claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 in view of the teachings by Wang *et al.*

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989.

Ladner *et al.* teach binding proteins displayed on the outer surfaces of filamentous phage or cells (please refer to column 1, lines 40-52). Ladner *et al.* teach that the display system may be

utilized to develop antibodies (please refer to column 15, lines 65-68) as further evidenced by Ladner *et al.* (U.S. Patent No. 4,949,778 issued August 7, 1990; column 8, lines 62-67, column 15, lines 45-52, column 33, lines 56-68, and column 34, lines 1-57). In addition, Ladner *et al.* teach V_L-linker-V_H as single-chain antigen-binding fragment and V_L-C_L bound to V_H-C_{H1} as fragment antibodies (e.g. present claims 1-4 and 6; please refer to column 15, lines 34-64). Furthermore, Ladner *et al.* teach the display system as a binding domain operably linked to a signal sequence (e.g. OmpA and present claim 17; please refer to column 61, lines 39-53, column 62, lines 31-33, and column 63, lines 28-48) and a coat protein (e.g. M13 gene III and present claims 18 and 25; please refer to column 51, line 51 and column 54, lines 48-50) so that the expression product is transported to the inner membrane of the host cell (e.g. *E. coli* and present claims 25 and 35; please refer to column 56, lines 6-14 and column 61, lines 21-23) and trapped until the single-stranded DNA of the nascent phage particle collects both the wild type coat protein and the hybrid protein from the lipid bilayer and packages the hybrid protein into the surface sheath of the filamentous phage (e.g. M13 and present claims 19-21 and 25-26; please refer to column 54, lines 37-38 and column 55, lines 36-60) thereby exposing the hybrid protein on the replicable genetic package (please refer to column 51, lines 33-68 and column 52, lines 1-11). Lander *et al.* also teach the use of flexible linkers that encode a recognition site for a specific protease including Factor Xa (e.g. present claims 11, 13, 16 and 30-31, please refer to column 57, lines 39-59, column 58, lines 1-18, column 70, lines 64-68, column 71, lines 1-5, and column 73, lines 20-40).

However, Lander *et al.* do not teach a disordered region cleavable by urokinase.

Goers et al. *et al.* teach attachment of a therapeutic agent to antibodies via a linker which may be cleavable by urokinase (e.g. please refer to column 3, lines 14-31). Goers *et al.* further teach that the linker can be an amine, a branched linker, proteolytic peptide linkers cleavable by urokinase, or a linker may have a spacer and a cleavable portion of a random construction (e.g. present claim 11, 29-31; please refer to columns 21-22, Tables III-V and VII-VIII, Example: Series IV-V). Therefore, Goers *et al.* specifically teaches a urokinase cleavable linker.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the antigen-binding polypeptide display system of Ladner *et al.* and incorporate the urokinase peptide cleavage sequences of Goers *et al.*

One having ordinary skill in the art would have been motivated to do this because Goers *et al.* teaches that the linkage of the therapeutic agent to the antibody may interfere with antigen binding and potentially reduce the effectiveness of the therapeutic system, therefore, the use of a cleavage site to release the therapeutic agent from the antibody would be beneficial (please refer to column 4, lines 7-27 of Goers *et al.*). Furthermore, Lander *et al.* teach the use of flexible linkers that encode a recognition site for a specific protease including Factor Xa (e.g. present claims 16 and 30-31, please refer to column 57, lines 39-59, column 58, lines 1-18, column 70, lines 64-68, column 71, lines 1-5, and column 73, lines 20-40). Therefore, a urokinase cleavable peptide linker taught by Goers *et al.* could be utilized to increase antigen binding by the proteins displayed by genetically replicable packages taught by Ladner *et al.*

There is a reasonable expectation of success in the modification of the antibody display system taught by Ladner *et al.* with the urokinase cleavage sequence of Goers *et al.* because of the examples in Goers *et al.* showing the success of urokinase cleavable linkers joining

antibodies to therapeutic agents or cells (please refer to sections 9.1-9.4 and 10.2-10.4 in Goers *et al.*).

Therefore, the modification of the antibody display system by Lander *et al.* with the urokinase cleavable sequence by Goers *et al.* would render the instant claims prima facie obvious.

17. Claims 1-4, 6, 11, 13, 16-21, 25-26, 29-31, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths *et al.* U.S. Patent No. 5,962,255 issued October 5, 1999 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989.

Griffiths *et al.* teach methods and recombinant host cells for the production of antibodies displayed on the surface of replicable genetic display packages or rgdps (e.g. filamentous phage) via vectors comprising nucleic acids encoding a first and second polypeptide for a specific binding pair or sbp (please refer to the "Abstract"). Griffiths *et al.* also teach the first polypeptide as the variable and constant regions of an antibody light chain (e.g. V_L and C_L), the second polypeptide as the variable and constant regions of an antibody heavy chain (e.g. V_H and C_H or V_H and C_{H1}) with a g3 anchoring peptide (e.g. pIII, gIII, or coat protein III; present claims 18 and 25) at the N-terminus, with an intervening sequence encoding a selectable "marker peptide" and a loxP site (e.g. a first polypeptide encoding V_L/C_L, a second polypeptide with a cleavable sequence, and a third polypeptide encoding V_H/C_H having an anchor peptide of present claims 1-4, 6, 16, 18, 25, and 30; please refer to Figures 3-4, 6-7, 14-19 and columns 19-21, 24, and 28). Griffiths *et al.* also teach the Cre recombinase which cleaves the loxP site of the intervening sequence and is expressed in a separate plasmid (e.g. enzymatic proteolytic agent of present claims 11, 13, and 30; please refer to column 52, lines 45-55 and column 53, lines 19-24). In

addition, Griffiths *et al.* teach that the replicable genetic display package can be a M13 bacteriophage or *E. coli* infected with an M13 bacteriophage (e.g. present claims 19-21, 25-26, and 35; please refer to column 7, lines 52-60, column 22, lines 59-67, and column 24, lines 3-35). Furthermore, Griffiths *et al.* teaches that a secretory leader peptide such as OmpA can be utilized to display the polypeptides (e.g. present claim 17; please refer to column 22, lines 65-66).

However, Griffiths *et al.* do not teach the use of urokinase as a proteolytic agent.

Goers et al. *et al.* teach attachment of a therapeutic agent to antibodies via a linker which may be cleavable by urokinase (e.g. please refer to column 3, lines 14-31). Goers *et al.* further teach that the linker can be an amine, a branched linker, proteolytic peptide linkers cleavable by urokinase, or a linker may have a spacer and a cleavable portion of a random construction (e.g. present claim 11; 29-31; please refer to columns 21-22, Tables III-V and VII-VIII, Example: Series IV-V). Therefore, Goers *et al.* specifically teaches a urokinase cleavable linker.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the display vectors of Griffiths *et al.* to incorporate a urokinase cleavable linker of Goers *et al.*

One having ordinary skill in the art would have been motivated to do this because Goers *et al.* teaches that although antibody carrier systems can be highly specific for the target site, a significant problem exists in that the therapeutic agent may not be released at the site and the linkage of the therapeutic agent to the antibody may interfere with antigen binding potentially reducing the effectiveness of the system, therefore, the use of a cleavage site to release the therapeutic agent from the antibody would be beneficial (please refer to column 4, lines 7-27).

Furthermore, Griffiths *et al.* teach that the displayed antibodies can be removed from the genetically replicable package via proteolytic cleavage of the protein (please refer to column 27, lines 59-67). Therefore, one having ordinary skill in the art would be motivated to utilize the urokinase specific cleavage sequences taught by Goers *et al.* to remove the antibodies from the genetically replicable package taught by Griffiths *et al.*

There is a reasonable expectation of success in the modification of the antibody display system of Griffiths *et al.* with the urokinase cleavable linker of Goers *et al.* because of the examples taught by Goers *et al.* show the success of using urokinase cleavable linkers with an antibody conjugated to cells (please refer to Examples 9.1-9.4 and 10.2-10.4 of Goers *et al.*).

Therefore, the modification of the antibody display system taught by Griffiths *et al.* with the teachings of urokinase cleavable linkers by Goes *et al.* render the instant claims prima facie obvious.

18. Claims 1-4, 6, 11, 13, 16-21, 25-26, 29-31, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang *et al.* U.S. Paten No. 6,833,441 B2 filed August 1, 2001 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989.

Wang *et al.* teach recombinant polynucleotides, vectors, and host cells for producing antigen-binding units (e.g. present claim 35; please refer to the "Abstract"). Wang *et al.* teach a light chain variable region fused to a heterodimerization sequence (e.g. first polypeptide), a "flexon" (e.g. second polypeptide), a heavy chain variable region fused to a second hetrodimerization sequence (e.g. third polypeptide) in a phage display vector and a host cell (e.g. present claims 1-3; please refer to column 4, lines 21-30, column 5, lines 48-61, column 6, lines 45-63,column 20, lines 1-15, column 26, lines 54-64, and column 38, lines 1-39). Additionally,

Wang *et al.* also teach V_L, V_H, C_L, C_H, and C_{H1} (e.g. present claims 4 and 6; please refer to column 12, lines 3-10). In addition, Wang *et al.* teach the phage display vector as the filamentous phage M13 and fusion of antibody peptides to a phage coat protein specifically pIII of M13 (e.g. present claims 18-21 and 25-26; please refer to column 13, lines 47-52 and column 29, lines 49-65). Furthermore, Wang *et al.* also teach the use of OmpA for display in bacterial host cells including *E. coli* (e.g. present claim 17 and 25; please refer to column 30, lines 39-49 and column 35, lines 16-22). Moreover, Wang *et al.* teach protease cleavage sites between the heterodimerization sequences and phage coat protein (e.g. present claims 11, 13, 16, and 30-31; please refer to column 37, lines 1-7).

However, Wang *et al.* does not teach urokinase as a proteolytic agent.

Goers et al. *et al.* teach attachment of a therapeutic agent to antibodies via a linker which may be cleavable by urokinase (e.g. please refer to column 3, lines 14-31). Goers *et al.* further teach that the linker can be an amine, a branched linker, proteolytic peptide linkers cleavable by urokinase, or a linker may have a spacer and a cleavable portion of a random construction (e.g. present claim 29-31; please refer to columns 21-22, Tables III-V and VII-VIII, Example: Series IV-V). Therefore, Goers *et al.* specifically teaches a urokinase cleavable linker.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the antibody phage display vector of Wang *et al.* with the urokinase peptide cleavage sequence of Goers *et al.*

One having ordinary skill in the art would have been motivated to do this because Wang *et al.* teach about the instability of single chain antigen binding proteins and the potential interference of peptide linker sequences with antigen binding (please refer to column 2, lines 7-

55 of Wang *et al.*). Furthermore, Goers *et al.* teaches that the linkage of the therapeutic agent to the antibody may interfere with antigen binding and potentially reduce the effectiveness of the therapeutic system, therefore, the use of a cleavage site to release the therapeutic agent from the antibody would be beneficial (please refer to column 4, lines 7-27 of Goers *et al.*). Therefore, a urokinase cleavable peptide linker taught by Goers *et al.* could be utilized to increase antigen binding by the proteins taught by Wang *et al.*

There is a reasonable expectation of success in the modification of the antibody phage display vector taught by Wang *et al.* with the urokinase cleavage sequence of Goers *et al.* because of the examples in Goers *et al.* showing the success of urokinase cleaving linkers joining antibodies to therapeutic agents or cells (please refer to sections 9.1-9.4 and 10.2-10.4 in Goers *et al.*).

Therefore, the modification of the antibopdy phage display vector of Wang *et al.* with the urokinase cleavable sequence by Goers *et al.* would render the instant claims prima facie obvious.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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ADS
October 20, 2005

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